

We Claim:

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1. An isolated polynucleotide comprising a nucleic acid segment encoding a human PAPS synthetase, said nucleic acid segment having a nucleotide sequence of (SEQ. ID. NO.:1), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these.
  2. The polynucleotide of Claim 1, wherein the nucleic acid segment is a gene-specific fragment comprising the nucleotide sequence of (SEQ. ID. NO.:9).
  3. The polynucleotide of Claim 1, wherein the nucleic acid segment is a DNA.
  4. The polynucleotide of Claim 1, wherein the nucleic acid segment is an RNA.
  5. The polynucleotide of Claim 1, wherein the nucleic acid segment is a chimeric RNA/DNA.
  6. A nucleic acid construct comprising a nucleic acid segment comprising:
    - (A) a nucleotide sequence of (SEQ. ID. NO.:1), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these; or
    - (B) a nucleic acid segment encoding a human PAPSS2 protein having an amino acid sequence of (SEQ. ID. NO.:7).
  7. The nucleic acid construct of Claim 6, wherein the nucleic acid segment has the nucleotide sequence of (SEQ. ID. NO.:9) or a sequence complementary thereto.
  8. The nucleic acid construct of Claim 6, wherein the nucleic acid segment is a probe or primer.
  9. The nucleic acid construct of Claim 6, wherein the nucleic acid segment is a DNA.
  10. The nucleic acid construct of Claim 6, wherein the nucleic acid segment is an RNA.
  11. The nucleic acid construct of Claim 6, wherein the nucleic acid segment is a chimeric RNA/DNA.
  12. The nucleic acid construct of Claim 6, wherein the nucleic acid segment is cloned into an expression vector.
  13. The nucleic acid construct of Claim 8, wherein the nucleic acid segment has a nucleotide sequence comprising 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.: 3), a complementary nucleotide sequence, or a PAPSS2-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

14. The nucleic acid construct of Claim 8, wherein the nucleic acid segment has a nucleotide sequence comprising 5'-CGGAAAGATGGCAACAATGG (SEQ. ID. NO.: 4), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

15. The nucleic acid construct of Claim 8, wherein the nucleic acid segment has a nucleotide sequence comprising 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.: 5), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

16. The nucleic acid construct of Claim 8, wherein the nucleic acid segment has a nucleotide sequence comprising 5'-TGCGAATGGAGAAATAAAGCTG (SEQ. ID. NO.: 6), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

17. An isolated polynucleotide comprising a nucleic acid segment encoding a murine PAPS synthetase, said nucleic acid segment having a nucleotide sequence of (SEQ. ID. NO.:2), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these.

18. The polynucleotide of Claim 17, wherein the nucleic acid segment is a gene-specific fragment comprising the nucleotide sequence of (SEQ. ID. NO.:10).

19. The polynucleotide of Claim 17, wherein the nucleic acid segment is a DNA.

20. The polynucleotide of Claim 17, wherein the nucleic acid segment is an RNA.

21. The polynucleotide of Claim 17, wherein the nucleic acid segment is a chimeric RNA/DNA.

22. A nucleic acid construct, comprising a nucleic acid segment comprising:

(A) a nucleotide sequence of (SEQ. ID. NO.:2), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these; or

(B) a nucleic acid segment encoding a human *PAPSS2* protein having an amino acid sequence of (SEQ. ID. NO.:8)

23. The nucleic acid construct of Claim 22, wherein the nucleic acid segment is a gene-specific fragment having the nucleotide sequence of (SEQ. ID. NO.:10).

24. The nucleic acid construct of Claim 22, wherein the nucleic acid segment is a probe or primer.

25. The nucleic acid construct of Claim 22, wherein the nucleic acid segment is a DNA.

26. The nucleic acid construct of Claim 22, wherein the nucleic acid segment is an RNA.

27. The nucleic acid construct of Claim 22, wherein the nucleic acid segment is a chimeric RNA/DNA.

28. An oligonucleotide primer for amplifying a *PAPSS2*-specific nucleic acid segment, comprising:

(A) (SEQ. ID. NO.:3), (SEQ. ID. NO.:4), (SEQ. ID. NO.:5), (SEQ. ID. NO.:6), (SEQ. ID. NO.:11), (SEQ. ID. NO.:12), (SEQ. ID. NO.:13), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15),  
5 (SEQ. ID. NO.:16), (SEQ. ID. NO.:17), (SEQ. ID. NO.:18), or (SEQ. ID. NO.:28);

(B) a nucleotide sequence complementary to (A);

(C) a *PAPSS2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end.

29. An oligonucleotide primer for amplifying a *Papss2*-specific nucleic acid segment, comprising:

(A) (SEQ. ID. NO.:19), (SEQ. ID. NO.:20), (SEQ. ID. NO.:21), (SEQ. ID. NO.:22),  
5 (SEQ. ID. NO.:23), (SEQ. ID. NO.:24), (SEQ. ID. NO.:25), (SEQ. ID. NO.:26), or (SEQ. ID. NO.:27);

(B) a nucleotide sequence complementary to (A);

(C) a *Papss2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end.

30. A pair of oligonucleotide primers comprising a forward and a reverse primer, said pair capable of producing detectable nucleic acid amplification products having:

(A) (SEQ. ID. NO.:1) or (SEQ. ID. NO.:9);

(B) a nucleotide sequence complementary to (A); or

5 (C) a *PAPSS2* gene-specific fragment of (A) or (B).

31. The pair of oligonucleotide primers of Claim 30, wherein the forward primer has a nucleotide sequence comprising 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.: 3), a complementary nucleotide sequence, or a *PAPSS2*-specific fragment of either of these at least 15 nucleotides long; and

5 the reverse primer has a nucleotide sequence comprising 5'-CGGAAAGATGGCAACAATGG-3' (SEQ. ID. NO.: 4), a complementary nucleotide sequence, or a *PAPSS2*-specific fragment of either of these at least 15 nucleotides long.

32. The pair of oligonucleotide primers of Claim 30, wherein the forward primer has a nucleotide sequence comprising 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.: 5), a complementary sequence, or a *PAPSS2*-specific fragment of either at least 15 nucleotides long; and

5 the reverse primer has a nucleotide sequence comprising 5'-TGCGAATGGAGAAATA AAGCTG-3' (SEQ. ID. NO.: 6), a complementary sequence, or a *PAPSS2*-specific fragment of either at least 15 nucleotides long.

33. The pair of oligonucleotide primers of Claim 30, wherein the forward primer comprises:

(A) (SEQ. ID. NO.:3), (SEQ. ID. NO.:5), (SEQ. ID. NO.:11), (SEQ. ID. NO.:12), or (SEQ. ID. NO.:13);

5 (B) a nucleotide sequence complementary to any of (A);

(C) a gene-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and

a reverse primer comprising:

10 (E) (SEQ. ID. NO.:4), (SEQ. ID. NO.:6), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15), (SEQ. ID. NO.:16), (SEQ. ID. NO.:17), or (SEQ. ID. NO.:18);

(F) a nucleotide sequence complementary to any of (E);

(G) a *PAPSS2*-specific fragment of (E) or (F) at least 15 nucleotides long; or

15 (H) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (E) or (F) at its 5' or 3' end.

34. A pair of oligonucleotide primers comprising a forward and a reverse primer, said pair capable of producing detectable nucleic acid amplification products having:

(A) (SEQ. ID. NO.:2) or (SEQ. ID. NO.:10);

(B) a nucleotide sequence complementary to (A); or

5 (C) a *Papss2* gene-specific fragment of (A) or (B).

35. The pair of oligonucleotide primers of Claim 34, wherein the forward primer comprises:

(A) (SEQ. ID. NO.:20), (SEQ. ID. NO.:22), (SEQ. ID. NO.:23), or (SEQ. ID. NO.:27);

(B) a nucleotide sequence complementary to any of (A);

5 (C) a *Papss2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and

the reverse primer comprises:

(E) (SEQ. ID. NO.:19), (SEQ. ID. NO.:21), (SEQ. ID. NO.:24), (SEQ. ID. NO.:25), or  
10 (SEQ. ID. NO.:26);

(F) a nucleotide sequence complementary to any of (E);

(G) a *Papss2*-specific fragment of (E) or (F) at least 15 nucleotides long; or

(H) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous  
nucleotide positions any sequence of (E) or (F) at its 5' or 3' end.

36. The pair of oligonucleotide primers of Claim 34, wherein

the forward primer has a nucleotide sequence comprising (SEQ. ID. NO.:20), a  
complementary nucleotide sequence, a gene-specific fragment of either of these at least 15  
nucleotides long; and

5 the reverse primer has a nucleotide sequence comprising (SEQ. ID. NO.:21), a  
complementary nucleotide sequence, or a gene-specific fragment of either of these at least 15  
nucleotides long.

37. A genetically modified vertebrate cell comprising the nucleic acid construct  
of Claim 6.

38. A genetically modified vertebrate cell comprising the nucleic acid construct  
of Claim 12.

5 39. A non-human vertebrate comprising the cell of Claim 37.

40. A non-human vertebrate comprising the cell of Claim 38.

41. An isolated PAPS synthetase protein comprising a polypeptide having an amino  
acid

10 sequence of (SEQ. ID. NO.:7), (SEQ. ID. NO.:8), or an antibody binding fragment of either of  
these at least 6 amino acids long.

42. A PAPSS2 fusion protein, comprising:

a first PAPSS2 polypeptide segment comprising an amino acid sequence of (SEQ. ID.  
NO.:7) or a gene-specific antibody binding fragment thereof at least 6 amino acids long; and  
a second predetermined polypeptide segment.

15 43. The fusion protein of Claim 42, wherein the PAPSS2 polypeptide segment is  
encoded by a nucleic acid segment having a nucleotide sequence of (SEQ. ID. NO.:9) or a  
gene-specific fragment thereof.

44. A *Papss2* fusion protein comprising:

20 a first *Papss2* polypeptide segment comprising an amino acid sequence of (SEQ. ID.  
NO.:8) or a gene-specific antibody binding fragment thereof at least 6 amino acids long; and

a second predetermined polypeptide segment.

45. The fusion protein of Claim 44, wherein the Papss2 polypeptide segment is encoded by a nucleic acid segment having a nucleotide sequence of (SEQ. ID. NO.:10), or a gene-specific fragment thereof.

46. A method of diagnosing spondyloepimetaphyseal dysplasia in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a *PAPSS2* gene, the presence of homozygosity for the variant allele of the gene corroborating a diagnosis of spondyloepimetaphyseal dysplasia in the human subject.

47. The method of Claim 46, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

48. The method of Claim 46, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

49. The method of Claim 48, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGC AACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

50. The method of Claim 48, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

51. The method of Claim 46, wherein the variant allele is characteristic of SEMD Pakistani-type.

52. A method of diagnosing spondyloepimetaphyseal dysplasia Pakistani-type in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of homozygosity for the variant allele corroborating a diagnosis of spondyloepimetaphyseal dysplasia Pakistani-type in the human subject.

53. The method of Claim 52, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

54. The method of Claim 52, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

55. The method of Claim 52, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGC AACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a PAPSS2-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a PAPSS2-specific fragment of any of these at least 15 nucleotides long.

56. The method of Claim 52, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a PAPSS2-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a PAPSS2-specific fragment of any of these at least 15 nucleotides long.

57. A method of diagnosing spondyloepimetaphyseal dysplasia Pakistani-type in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products, using at least one oligonucleotide primer having a sequence that comprises (SEQ. ID. NO.: 3), (SEQ. ID. NO.:4), (SEQ. ID. NO.:5), (SEQ.

10 ID. NO.:6), a sequence complementary to any of these, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long; and

15 b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of homozygosity for the variant allele corroborating a diagnosis of spondyloepimetaphyseal dysplasia Pakistani-type in the human subject.

58. The method of Claim 57, wherein analyzing the amplification products comprises digesting the amplification products with a *Hinc* II restriction endonuclease.

59. The method of Claim 57, wherein the sample is blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

60. A method of identifying a human carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia, comprising:

5 a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject without a symptom of spondyloepimetaphyseal dysplasia, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

10 b) analyzing the amplification products for the presence of a variant allele of a gene encoding a PAPS synthetase, the presence of the variant allele of the gene identifying the human subject as a carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia.

61. The method of Claim 60, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

62. The method of Claim 60, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

5 63. The method of Claim 62, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGC AACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

64. The method of Claim 62, wherein the oligonucleotide primer has a nucleotide



sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAAATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

65. The method of Claim 61, wherein the variant allele is characteristic of spondyloepimetaphyseal dysplasia Pakistani-type.

66. A method of identifying a human carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia Pakistani-type, comprising:

- a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject without a symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and
- b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of the variant allele of the gene identifying the human subject as a carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia Pakistani-type.

67. The method of Claim 66, wherein the sample is blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

68. The method of Claim 66, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

69. The method of Claim 68, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGCAACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

70. The method of Claim 68, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAAATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous

- 5 nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

71. The method of Claim 66, wherein analyzing the amplification products comprises digesting the amplification products with a *Hinc* II restriction endonuclease.

72. The method of Claim 66, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

73. A gene therapy method for treating a human subject having an osteoarthritic disorder, comprising:

- 5 exposing a cell derived from a tissue of a human subject having at least one symptom of an osteoarthritic disorder that is caused or aggravated by deficient enzymatic sulfation activity to a gene delivery mixture comprising at least one gene delivery agent and a nucleic acid construct having a segment encoding a PAPS synthetase protein comprising an amino acid sequence of (SEQ. ID. NO.:7) or (SEQ. ID. NO.:8), said construct being DNA and further comprising a promoter sequence, operable in the cell, operatively linked in a transcriptional unit to the sequence encoding the PAPS synthetase protein;
- 10 causing said nucleic acid construct to be taken up by, and released into, the cell so that said polynucleotide is incorporated into the genome of the cell, whereby expression of functional PAPS synthetase is enhanced in the cell; and
- 15 implanting the cell into the tissue of the human subject, whereby PAPS synthetase activity in said tissue is enhanced and at least one symptom of the osteoarthritic disorder in the human subject is improved.

74. The gene therapy method of Claim 73, wherein the osteoarthritic disorder is spondyloepimetaphyseal dysplasia, Stickler syndrome, spondyloepiphyseal dysplasia, achondrogenesis, achondroplasia, chondrodysplasia, diastrophic dysplasia, pseudoachondroplasia, or multiple epiphyseal dysplasia.

75. The gene therapy method of Claim 73, wherein the cell is a chondrocyte, hepatocyte, epithelial, or hemopoietic precursor cell.

76. The gene therapy method of Claim 73, wherein the cell is a chondrocyte and the tissue comprises a cartilage-forming tissue.

77. The gene therapy method of Claim 73, wherein the cell is a hemopoietic precursor cell and the tissue is bone marrow.

78. The gene therapy method of Claim 73, wherein the cell is a hepatocyte, and the tissue is liver.

79. The gene therapy method of Claim 73, wherein the cell is an epithelial cell, and the tissue is vascular epithelium.

80. A gene therapy method for treating a human subject having an osteoarthritic disorder, comprising:

5 exposing a cell derived from a tissue of a human subject having at least one symptom of an osteoarthritic disorder that is caused or aggravated by deficient enzymatic sulfation activity to a nucleic acid construct comprising a nucleic acid segment of a *PAPSS2* gene comprising a nucleotide sequence of (SEQ. ID. NO.:9), (SEQ. ID. NO.:10), or a gene-specific fragment of either of these, said construct being a chimeric RNA/DNA;

10 causing said nucleic acid construct to be taken up by, and released into, the cell so that said nucleotide sequence is incorporated into the genome of the cell, whereby expression of functional PAPS synthetase protein is enhanced in the cell; and

implanting the cell into the tissue of the human subject, whereby PAPS synthetase activity in said tissue is enhanced and at least one symptom of the osteoarthritic disorder in the human subject is improved.

81. The gene therapy method of Claim 80, wherein the osteoarthritic disorder is spondyloepimetaphyseal dysplasia, Stickler syndrome, spondyloepiphyseal dysplasia, achondrogenesis, achondroplasia, chondrodysplasia, diastrophic dysplasia, pseudoachondroplasia, or multiple epiphyseal dysplasia.

82. The gene therapy method of Claim 80, wherein the cell is a chondrocyte, hepatocyte, epithelial, or hemopoietic precursor cell.

83. The gene therapy method of Claim 80, wherein the cell is a chondrocyte and the tissue comprises a cartilage-forming tissue.

84. The gene therapy method of Claim 80, wherein the cell is a hemopoietic precursor cell and the tissue is bone marrow.

85. The gene therapy method of Claim 80, wherein the cell is a hepatocyte, and the tissue is liver.

86. The gene therapy method of Claim 80, wherein the cell is an epithelial cell, and the tissue is vascular epithelium.

87. A genetic testing kit for diagnosing SEMD in a human subject or for identifying a human carrier of SEMD, said kit comprising an oligonucleotide primer(s) comprising:

(A) a nucleotide sequence of (SEQ. ID. NO.:3), (SEQ. ID. NO.: 4), (SEQ. ID. NO.:5),

(SEQ. ID. NO.:6), (SEQ. ID. NO.: 11), (SEQ. ID. NO.: 12), (SEQ. ID. NO.:13), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15), (SEQ. ID. NO.:16), (SEQ. ID. NO.:17), (SEQ. ID. NO.:18), or (SEQ. ID. NO.:28);

(B) a nucleotide sequence complementary to (A);

(C) a *PAPSS2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.

88. A genetic testing kit for diagnosing spondyloepimetaphyseal dysplasia in a human subject or for identifying a human carrier of spondyloepimetaphyseal dysplasia, comprising the pairs of oligonucleotide primers of Claim 30; and

instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.

89. A genetic testing kit for diagnosing spondyloepimetaphyseal dysplasia in a human subject, or for identifying a human carrier of spondyloepimetaphyseal dysplasia, comprising the pair of oligonucleotide primers of Claim 33; and

instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.

90. A kit for genetically modifying a vertebrate cell, comprising a polynucleotide that comprises a *PAPSS2* sequence having (SEQ. ID. NOS.:1), a sequence complementary thereto, or a degenerate coding sequence thereof, or a gene-specific fragment of any of these; and instructions for using the polynucleotide for genetically modifying a vertebrate cell.

91. The kit of Claim 90, further comprising a gene delivery agent.

92. The kit of Claim 90, wherein the polynucleotide further comprises a promoter sequence operatively linked in a transcriptional unit to a nucleic acid segment encoding a *PAPSS2* protein having an amino acid sequence of (SEQ. ID. NO.:7).

93. The kit of Claim 90, wherein the polynucleotide is a chimeric RNA/DNA

94. A kit for genetically modifying a vertebrate cell, comprising a polynucleotide that comprises a *Papss2* sequence having (SEQ. ID. NOS.:2), a sequence complementary thereto, or a degenerate coding sequence thereof, or a gene-specific fragment of any of these; and instructions for using the polynucleotide for genetically modifying a vertebrate cell.

95. The kit of Claim 94, further comprising a gene delivery agent.

96. The kit of Claim 94, wherein the polynucleotide further comprises a promoter sequence operatively linked in a transcriptional unit to a nucleic acid segment encoding a PAPSS2 protein having an amino acid sequence of (SEQ. ID. NO.:8).

97. An isolated antibody or antibody fragment, comprising an antibody or antibody fragment that selectively binds a PAPS synthetase protein that has an amino acid sequence of (SEQ. ID. NO.:7) or (SEQ. ID. NO.8), or that selectively binds an antibody binding fragment of either of these at least 6 amino acids long.

98. The antibody or antibody fragment of Claim 97, wherein the antibody is a monoclonal antibody.

99. The antibody fragment of Claim 97, being a Fab', F(ab')<sub>2</sub>, or F(v) fragment.

100. The nucleic acid construct of Claim 6, further comprising a reporter gene.

101. The nucleic acid construct of Claim 22, further comprising a reporter gene.

102. The PAPSS2 fusion protein of Claim 42, wherein the second polypeptide segment is an human immunodeficiency virus TAT protein.

103. The PAPSS2 fusion protein of Claim 43, wherein the second polypeptide segment is an human immunodeficiency virus TAT protein.

104. A protein therapy method for treating a human subject having an osteoarthritic disorder, comprising:

exposing a cell of a tissue of a human subject having an osteoarthritic disorder that is caused or aggravated by deficient enzymatic sulfation activity to a fusion protein comprising a first PAPSS2 polypeptide segment that comprises an amino acid sequence of (SEQ. ID. NO.:7), or an enzymatically active fragment thereof, and a second polypeptide segment capable of infiltrating the cell, whereby the fusion protein is taken up by the cell and the PAPSS2 polypeptide segment is enzymatically active therein.

105. The protein therapy method of Claim 104, wherein the second polypeptide segment is an human immunodeficiency virus TAT protein.

106. The protein therapy method of Claim 104, wherein the osteoarthritic disorder is spondyloepimetaphyseal dysplasia, Stickler syndrome, spondyloepiphyseal dysplasia, achondrogenesis, achondroplasia, chondrodysplasia, diastrophic dysplasia, pseudoachondroplasia, or multiple epiphyseal dysplasia.

107. A kit for the treatment of osteoarthritic disorders caused or aggravated by deficient enzymatic sulfation activity, comprising:

a fusion protein comprising a first PAPSS2 polypeptide segment that comprises an amino acid sequence of (SEQ. ID. NO.:7), or an enzymatically active fragment thereof, and a second  
5 polypeptide segment capable of infiltrating the cell; and

instructions for using the fusion protein for treating osteoarthritic disorder(s) caused or aggravated by deficient enzymatic sulfation activity.

108. The kit of Claim 107, wherein the second polypeptide segment is an human immunodeficiency virus TAT protein.

*See  
Sect B4*